Hereditary hemorrhagic telangiectasia associated epistaxis in the Norwegian population.
Severity, impact on the quality of life and new treatment modality.

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Sinan Dheyauldeen

Contents:

Preface

This dissertation is about hereditary hemorrhagic telangiectasia (HHT) associated epistaxis. It proposes a new grading system for HHT associated epistaxis, and describes the grade of epistaxis and its impact on the quality of life in the Norwegian HHT population. It also discusses the early result of a new technique of intranasal injection of bevacizumab in treating HHT associated epistaxis. The results and conclusions of the following publications are presented and discussed:

Original articles:

I. Al-Deen S, Bachmann-Harildstad G. A grading scale for epistaxis in hereditary haemorrhagic teleangectasia. Rhinology 2008 Dec;46(4):281-4.

II. Dheyauldeen S, Abdelnoor M, Bachmann-Harildstad G. The natural history of epistaxis in patients with hereditary hemorrhagic telangiectasia in the Norwegian population: a cross-sectional study. Am J Rhinol Allergy 2011 Jul;25(4):214-8.

III. Geirdal AO, Dheyauldeen S, Bachmann-Harildstad G, Heimdal K. Quality of life in patients with hereditary hemorrhagic telangiectasia in Norway: A population based study. Am J Med Genet A 2012 Apr 23.

IV. Dheyauldeen S, Ostertun GA, Osnes T, Vartdal LS, Dollner R. Bevacizumab in hereditary hemorrhagic telangiectasia-associated epistaxis: effectiveness of an injection protocol based on the vascular anatomy of the nose. Laryngoscope 2012 Jun;122(6):1210-4.

My role in paper III, as a second author, was to measure the epistaxis grade of the included patients, according to the grading system proposed in paper I. I have also been involved in planning the study design. In addition, I reviewed and updated the clinical manifestation, diagnostic criteria and the genotype of the included patients and participated in writing the introduction and results of the article and in discussing the results.

Abbreviations and acronyms:

ALK1	Activin-receptor-like kinase 1.
AVF	Arteriovenous fistulae.
AVM	Arteriovenous malformation.
BP	Bodily pain.
CL	Cantril's Self-Anchoring Ladder.
CT	Computed tomography.
CAVM	Cerebral arteriovenous malformation.
CNS	Central nervous system.
ENG	Endoglin.
ESS	Epistaxis severity score.
GH	General health.
GI	Gastrointestinal.
HAVM	Hepatic arteriovenous malformation.
HHT	Hereditary hemorrhagic telangiectasia.
HR-QoL	Health related quality of life.
IFT	Intensity, frequency and transfusion epistaxis grading system.
JPHT	Syndrome of juvenile polyposis and HHT.
MCS	Mental component scale.
MH	Mental health.
MRI	Magnetic resonance imaging.
PAVM	Pulmonary arteriovenous malformation.
PCS	Physical component scale.
PF	Physical function.

10QoL	Quality of life.
RE	Role limitation due to emotional problems.
RP	Role limitation due to physical problems.
SD	Standard deviation.
SF	Social functioning.
SF-36	Short form 36.
SFB-HHT	HHT-Symptomspezifischer Fragebogen (German) = HHT-Symptom specific questionnaire (English).
STROBE	The strengthening the reporting of observational studies in epidemiology.
TGFβ-BMP	Transforming growth factor beta – bone morphogenic protein.
VEGF	Vascular endothelial growth factor.
VT	Vitality.

Chapter 1

1.1 Introduction:

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu–Osler–Weber disease, is a rare, vascular disorder with autosomal dominant inheritance pattern, characterized by vascular abnormalities in the form of mucosal and cutaneous telangiectases and arteriovenous malformations (AVM). Recurrent bleedings from telangiectases, most commonly in the form of epistaxis and less commonly in the form of gastrointestinal (GI) bleedings, are characteristic of the disease. Arteriovenous malformations can be found in the lungs, liver, and central nervous system (CNS). Life threatening visceral bleedings from AVMs of the lung, liver and CNS are also known clinical findings.

1.1.1 Clinical features:

Epistaxis:

Spontaneous recurrent epistaxis from telangiectases in the nasal mucosa is the most common clinical manifestation of HHT (1-4). Nosebleeds are the first clinical symptom of the disease in about 80% of cases (5;6). The severity and frequency of epistaxis is highly variable even within the same family (1;7).

Mucocutaneous telangiectases:

Telangiectases of the skin and oral mucous membrane occur in 50-90% of HHT individuals (2;5;8-10). It usually presents later in life than epistaxis and increases in size and number with age (11). They typically occur in the face, lips, buccal mucosa, tongue, fingertips, hand, ears

and chest, but can occur elsewhere (2;5). They may bleed but rarely to a degree of clinical significance (2;12).

Gastrointestinal tract:

Mucosal telangiectases in the GI tract may lead to recurrent upper or lower GI bleeding in 15-33% of HHT patients (10;11;13). They present with iron deficiency anemia, and occasionally with acute GI (2;10). The prevalence of GI telangiectases, including non-symptomatic telangiectases, is still doubtful (14;15). Some studies showed a prevalence of 75-86% (16;17).

Liver:

Asymptomatic hepatic AVM (HAVM) occurs in 30-74% of HHT patients (18-23). Symptomatic hepatic involvement is less common (9;23). Symptomatic liver involvement includes: high output heart failure secondary to intrahepatic shunt, portal hypertension, biliary disease, and portal encephalopathy (21;24-27).

Lung:

The prevalence of pulmonary arteriovenous malformations (PAVMs) in HHT patients depends on the method used for detection and the gene mutation type (28). Based on chest CT scan and/or pulmonary angiography, the PAVM can be detected in 26-56% of HHT patients (8;9;15;29-32), with a prevalence of 49-75% among HHT1 subtype and 5-44% among HHT2 subtype (9;15;29;30). A recent study showed positive intrapulmonary shunt in 85% of HHT1 patients, and 35% of HHT2 patients using contrast echocardiography, compared to 7% in the control population (30).

Pulmonary arteriovenous malformations lead to hypoxaemia because of the pulmonary right-to-left shunt effect. The lack of the filtering effect of the pulmonary capillary bed allows small

emboli to reach the systemic circulation, particularly the cerebral circulation. In addition, the fragile vessels of these AVMs can bleed into the bronchial tree or the pleural cavity (2).

The other type of lung affection in HHT is the rare pulmonary arterial hypertension which occurs predominantly in HHT2 patients (33;34).

Central nervous system (CNS):

Typical primary HHT related affection of the brain varies from cerebral arteriovenous malformations (CAVMs), arteriovenous fistulae (AVFs), microAVMs (measuring <1 cm in size) and capillary telangiectases (35;36). These can be found in approximately 23% of HHT patients on screening (35). Symptoms associated with these lesions include headache, seizures, ischaemia of the surrounding tissue due to a steal effect, or hemorrhage(2).

Other CNS related clinical manifestations including migraine, brain abscess, transient ischemic attack, and stroke are usually complication of PAVM (secondary cerebral affection). Pulmonary AVMs are the source of cerebral involvement in 2/3 of the cases in whom neurological symptoms develop (37).

Spinal AVMs are significantly less common than brain AVMs and usually present with paralysis and/or complaint of back pain (28).

1.1.2 History:

The word telangiectasia was first used by the ophthalmologist Carl Ferdinand Graefe in 1808 to describe small vessels anomalies (38;39). The earliest publications of the disease were by Sutton in 1864 (40) and Babington in 1865 (41) who described several families with epistaxis without using the word “telangiectasia”. Rendu in 1896 described the disease as recurrent nosebleed with cutaneous angiomas (42). Osler described in 1901 families with recurrent

epistaxis with cutaneous and mucous membrane telangiectases and differentiated the disease from hemophilia (43). In 1907, Weber described the disease as hereditary angiomas with recurrent epistaxis (44). Hanes (45) described in 1909 for the first time the histopathological aspect of the disease, and he is regarded as the forgotten man in Rendu-Osler-Weber disease (39;46). In 1994, *ENG* mutation in chromosome 9 outlined as the cause of HHT type 1 (47). *ALK1* mutation in chromosome 12 was described as a cause of HHT type 2 in 1996 (48). The diagnostic criteria, known as Curaçao Criteria were developed in 1999 and published in 2000 (49). The criteria were validated and were included in the international guidelines for diagnosis and management of HHT in 2009 (34;35;50). Elevated level of VEGF in the serum of HHT patients has been described for the first time in 2003 (51).

1.1.3 Epidemiology:

Hereditary hemorrhagic telangiectasia is a rare disease with a prevalence of 1 in 5-8000 people (52-54). The disease has wide geographical and ethnic distribution (5).

Although it is an autosomal (non-sex linked) disease, with an expected female to male ratio is 1:1, most of the studies show a higher female to male ratio (1;3;11;29;55;56). This is most likely because of recruitment bias due to the fact that females are usually more oriented to self health care than males. Other possible explanations are the chronic blood loss due to menstruation or the hormonal factor, which can lead to more obvious symptoms and earlier diagnosis in females than males.

1.1.4 Genetics:

Hereditary hemorrhagic telangiectasia is an autosomal dominant inherited disease, its penetrance increasing with age (57). The affected individuals are heterozygous. Homozygous forms are lethal and associated with intrauterine or infantile death (58-60). Mutation at Endoglin (*ENG*) gene in chromosome 9 and mutation at activin-receptor-like kinase 1 (*ALK1*) gene in chromosome 12 are responsible for 90% of the HHT cases (5;57). These two genes account for the two types of the disease, which are known as HHT1 and HHT2 respectively. A third and forth disease causative loci with still unknown genes have been described in chromosome 5 (61) and chromosome 7 (62). Mutation at *SMAD4* gene in chromosome 18 leads to the syndrome of juvenile polyposis and HHT known as JPHT (63).

1.1.5 Pathogenesis:

Telangiectases are small dilated blood vessels near the surface of the skin or mucous membranes, measuring between 0.5 and 1 millimeter in diameter. Longitudinal studies, investigating the natural course of the telangiectases, do not currently exist. However, it has been emphasized that the earliest morphologic change in the pathogenesis of HHT appears to be focal dilatation of postcapillary venules. As the venules increase in size, in both luminal diameter and vascular wall thickness, they become convoluted and connect to enlarging arterioles through capillary segments. Eventually these segments disappear, leading to direct arteriovenous communication. In telangiectasis, most venules show excessive layers of smooth muscle cells without any elastic fibers or have an incomplete layer of smooth muscle cells. Similar to telangiectases, AVMs lack capillaries and consist of direct connections between arteries and veins, but are much larger in size (5;64).

Both *ENG* and *ALK1* genes encode proteins involved in signaling by the transforming growth factor beta – bone morphogenic protein (TGFβ-BMP) super-family in the vascular endothelial

cells (5;7). TGFβ-BMP regulates cellular growth, differentiation and wound repair through signal transduction cascades from transmembrane receptor complexes (5). The abnormal vessels in HHT develop because of abnormal TGFβ-BMP signaling during vascular development and homoeostasis (2;5;34;65). This leads to the persistence of the activation phase of angiogenesis where angiogenic factors, such as the vascular endothelial growth factor (VEGF), are produced and play a potential role in angiodysplasia (65).

1.1.6 Diagnosis:

There are no biochemical tests for HHT and the diagnosis is clinical and depends on four diagnostic criteria, known as Curaçao Criteria, which were developed in 1999 (49) (Table 1). The Curaçao criteria were validated in 2009 (35;50). According to these criteria, a person is diagnosed with "definite HHT" when having three or four criteria; "suspected HHT" when having two criteria and "unlikely HHT" when only one criterion is present.

Genetic tests for *ENG, ALK1* and *SMAD4* genes are available. They are used to clarify the specific HHT mutation in an HHT family, allowing diagnosis among those relatives (often children and young adults) who do not meet clinical diagnostic criteria (34;35). The genetic tests are negative in 15-20% of HHT families (8;49;66).

1.1.7 Screening:

Screening in HHT refers to testing members of HHT families (who may or may not be symptomatic for other aspects of the disease) for the presence of silent disease manifestations such as pulmonary, hepatic or cerebral AVMs (34).

Screening for pulmonary, hepatic and cerebral AVMs are recommended according to the international guidelines (35).

Pulmonary screening has been recommended for all patients with possible or confirmed HHT (12;35;67;68). The recommended initial screening test for PAVM is transthoracic contrast echocardiography. Positive screening should be confirmed with unenhanced multidetector thoracic CT scan with thin-cut (e.g. 1-2mm) reconstructions (35).

Screening for hepatic AVM are recommended to clarify the diagnosis of HHT using Doppler Ultrasound, in patients with 1 or 2 HHT diagnostic criteria and in whom genetic testing is either inconclusive or unavailable. The international guidelines also recommend screening for cerebral AVMs by cerebral MRI (35).

Children of a parent with HHT who do not meet the diagnostic criteria should be considered to have the disease for purposes of screening unless excluded by genetic test (35;69).

1.1.8 Treatment:

Correcting the gene defect in *ENG, ALK1* or *SMAD4* by gene therapy is not yet available. The applicable therapies now can be summarized in four groups:

1. Compensation therapy: to compensate for blood loss by repeated red packed cell transfusions and iron supplements.
2. Obliteration or removal of the affected vessels: this includes embolization therapy for pulmonary and cerebral AVMs and feeding arteries for nasal mucosa. This therapy category includes also the surgical resection of the cerebral AVM, replace the nasal septum mucosa by skin (septodermoplasty) and laser therapy for telangiectases. It includes also organ (liver) transplantation (70;71).

3. Prevention of excessive bleeding by the use of prothrombotic therapy as antifibrinolytic (e.g. tranexamic acid) (72) or hormonal therapy (e.g. Tamoxifen and Raloxifin) (73).
4. Revise or correct the abnormal vascular response by anti-angiogenesis (Bevacizumab) (74), or molecules stimulating vessel maturation (Thalidomide) (75).

1.1.9 Prognosis:

Hereditary hemorrhagic telangiectasia is associated with a shorter life expectancy and early mortality. Although maternal complication can lead to death of young women at childbirth due to hemorrhage from pulmonary or cerebral AVMs in a few cases (14;54), a statistically significant difference in the life expectancy between gender and gene mutation subgroups of the disease has not been demonstrated (54;76).

The decrease in life expectancy can approach 7 years (76). This early mortality is usually due to major acute complications (54;76).

Chapter 2:

2.1 Background

2.1.1 HHT associated epistaxis:

Epistaxis is usually the first and most common symptom in HHT. Eighty to 100 percent of the HHT patients suffered from epistaxis (6;11;29;31). Epistaxis is the first symptom of the disease in about 80-90% of the patients (3;5). The majority of the patients start to experience recurrent nosebleed during the first two decades of life (1;3;11;56). Although AVMs are the most life threatening pathologies for patients with HHT, epistaxis is the most annoying symptom. It has the greatest negative impact on health-related Quality of Life (QoL) (4;77-79). Hereditary hemorrhagic telangiectasia associated epistaxis is characterized by being recurrent, spontaneous or easily provoked by bending over, sneezing, running or emotional stress (1;2;7). The HHT associated epistaxis can be functionally and socially debilitating for the patient (80), it can affect almost all aspects of life and lead to secondary health problems like iron deficiency anemia, shortness of breath and malaise (3).

2.1.2 The severity of HHT associated epistaxis:

The clinical features of HHT, including epistaxis severity, are highly variable, show ethnic and geographical variations (81), and vary even among members of the same family (7). Seasonal and diurnal variations of epistaxis associated with HHT have been described (82). Different systems have been used to score HHT associated epistaxis (83). Recently, an

epistaxis severity score (ESS) was proposed, sponsored by the HHT Foundation International (84). There is still no common internationally accepted grading system for epistaxis in HHT.

2.1.3 Treatment of HHT associated epistaxis:

A wide variety of treatment options have been developed for control of epistaxis in HHT (78) (Table 3). Many of these modalities are expensive and almost all of them have side effects, drawbacks and limitations. Choosing the appropriate modality for each patient depends extensively on the severity of the epistaxis.

2.1.4 HHT in Norway:

The HHT team at Oslo University Hospital - Rikshospitalet is a multidisciplinary working group representing the only "HHT center of excellence" in Norway. It aims to improve the diagnosis, treatment and follow-up procedures for patients with HHT in Norway. The team represents collaboration between the Department of Medical Genetics, Department of Otorhinolaryngology, Department of Pulmonary Medicine, Gastroenterology Department, Radiology Department, Department of Neurosurgery, Department of Dermatology, Department of Blood Diseases and Center for Rare Disorders. The team meets regularly to discuss treatment and research projects on HHT.

Patients with clinical suspicion of HHT are referred to the team from all over the country. These are usually patients with recurrent epistaxis, newly diagnosed AVMs, patients with GI bleeding in whom the endoscopic examination revealed GI telangiectases or asymptomatic relatives of HHT patients.

In 2006, the HHT patients' database was established for quality assurance and research. In December 2011 there were 250 patients registered in the database. Included in the database are patients with definite clinical diagnosis (with 3-4 diagnostic criteria), patients with unlikely or suspected clinical diagnosis (with 1-2 diagnostic criteria) with a positive *ENG*, *ALK1* or *SMAD4* gene mutation test, and asymptomatic first degree relatives with a positive *ENG* or *ALK1* gene mutation test.

2.2. Purpose of thesis:

Effectiveness of treatment of HHT associated epistaxis depends on choosing the appropriate treatment modality for each patient. This in turn depends on the severity of epistaxis in each patient, its impact on QoL, and co-morbidity. In this dissertation, a grading system for HHT associated epistaxis is proposed and the natural history of epistaxis and its impact on QoL was investigated. A second objective was to study the effectiveness of a new treatment modality in the treatment of HHT associated epistaxis. The necessity of this work came from:

1. Different institutions are using different treatment modalities and different grading systems for the severity of epistaxis in HHT (78;85-87). This makes it difficult to compare and evaluate the effectiveness of different treatment modalities in treating epistaxis of different grades. The aim was therefore to propose a grading system that can be the base for an internationally accepted system.
2. Understanding the natural history of epistaxis in HHT is important to predict who the high-risk patients are and to prevent complications. Most of the studies focus on the treatment modalities of the disease. Few studies highlight the natural history of HHT associated epistaxis, and most of these studies (1;11;46;55;56;87-89) were performed before the approval of the Curaçao diagnostic criteria. The natural history of HHT

associated epistaxis in the Norwegian population has not been studied before. The aim was to study the natural history of HHT associated epistaxis in the Norwegian population and to compare the results with studies from populations in other countries.

3. The impact of HHT associated epistaxis on QoL has a role in treatment decision. This impact has been studied in the United Kingdom (4;77-79), Germany (90;91), Greece (92) and Italy (79) but not in Norway. The aim was to study the impact of HHT associated epistaxis on QoL in the Norwegian population as a cross sectional study. The results of this study can be used in the future as a base-line to evaluate the effectiveness of new treatments.
4. The recent advance in understanding of the molecular base of the HHT pathogenesis opened the door for new possible medical therapies of the disease. The most recent of these therapies is bevacizumab (75;93). This study presents our early experience in using bevacizumab as intranasal injection in treating HHT associated epistaxis.

Chapter 3:

3.1 Aims of the study:

3.1.1 Paper I

The aim of paper I was to find a grading system for HHT associated epistaxis, which may serve as a proposal for an internationally accepted system. The aimed system is essential for better comparison of the results of different research groups. It is also important to judge the effectiveness of different treatment modalities used by different centers.

3.1.2 Paper II

The aim of paper II was to study the natural history of HHT associated epistaxis in the Norwegian population in relation to gender, age, gene mutation, age of onset of epistaxis and effect of treatment. This was important for the following purposes:

1. Better understanding of the natural history of HHT associated epistaxis generally.
2. The result of this cross sectional study might be the base for a future longitudinal study.
3. To compare the severity of epistaxis in the Norwegian population with populations in other countries.
4. The results of this study can be used as a base-line for future researches concerning HHT associated QoL and the efficacy of different treatment modalities in treating HHT associated epistaxis.

3.1.3 Paper III

The aim of paper III was to assess QoL in HHT patients in Norway by analyzing different levels of QoL: overall-, health-related and disease-specific QoL, taking into account demographic- and clinical variables. The reason for looking for all three levels of QoL was to examine how the HHT patients subjectively experienced overall and disease specific QoL, and how QoL is compared to normative population, using a generic health-related QoL measure.

3.1.4 Paper IV

Paper IV aimed to introduce and evaluate the effectiveness of a new method of intranasal bevacizumab injection in treating HHT associated epistaxis, based on the nasal vascular anatomy. The effect of local bevacizumab on epistaxis was measured using the IFT and the ESS grading systems.

Chapter 4:

4.1 Materials and methods

4.1.1 Materials

4.1.1.1 Paper I

The materials of the first paper were the main four different grading systems which had been used in different studies, the opinions of experts in the field of rhinology, and our experience in treating and follow up HHT patients at the Department of Otorhinolaryngology, Head and Neck Surgery in Oslo University Hospital-Rikshospitalet.

4.1.1.2 Paper II

One hundred and sixty patients have been included in the HHT research data base at HHT center at Oslo University Hospital / Rikshospitalet. One hundred and nine patients fulfilled three or four Curaçao criteria by the 1st of January 2009. Eleven patients were excluded because they were unavailable for follow up. Ninety-eight patients were contacted during the period from 01.01.2007 to 30.06.2009 either by direct consultation or telephone interview. The total group of patients (n=98) was divided into two subgroups: “the untreated group” (n=47) which included patients who had not been treated for epistaxis locally in the nose during the last 2 years and were not operated with septodermoplasty previously and “the treated group” (n=51) which included patients who were surgically treated for epistaxis with pulsed dye laser, diode laser, argon plasma coagulation, electro- or chemo-cauterization, septodermoplasty or a combination of these treatment modalities, during the last two years.

As it is a cross sectional study, the STROBE statement (94) recommendations have been followed.

4.1.1.3 Paper III

The patients: included patients were those with *ENG* or *ALK1* mutation and/ or having three or more Curaçao criteria for HHT, and older than 16 years at the time of genetic counseling. All included patients had given a written informed consent.

Ninety-five patients with HHT were invited to participate in the study. Sixty-six patients responded (response rate 71%) comprised of 39 women and 27 men.

Normative sample: 990 individuals of the 3648 individuals, who were included in Survey of Level of Living by Statistic Norway which had been carried out in 2002, were randomly drawn matching the age and gender of the patients group (15 controls per HHT patient).

4.1.1.4 Paper IV

The IFT grade of all patients, who had been treated for their HHT associated epistaxis during the last three years prior to this study, was recorded before each treatment. These treatments included: pulsed dye laser, diode laser or argon plasma coagulation. Many of these patients have been treated and followed up in our department for a much longer period of time but the IFT grading was available only for the last three years. The indications for inclusion in this study were clinical. The most common indication was the lack of clinical benefit, on the level of IFT grading, during the last 2-3 years in spite of increasing the frequency of the laser therapy, and additional medical therapy (Table 5).

Eight patients, with definite HHT diagnosis according to Curaçao diagnostic criteria, were included in the study. Five of the eight patients were females. The mean age was 56.5 years (SD =12.7, range 36 – 71). All patients had been previously treated for their HHT associated

epistaxis, with repeated pulsed-dye laser, diode laser, or argon plasma cauterization. Additional medical therapy, like oral and topical tranexamic acid, oral tamoxifen or raloxifen, and topical estrogen, were tried (Table 5). One of the patients was previously operated with septodermoplasty. Seven of the patients needed oral or intravenous iron supplement. Two of the included patients had nasal septum perforation from before.

Three out of the eight patients complained of HHT related gastrointestinal bleeding, three had pulmonary AVMs, one patient had HHT related pulmonary hypertension with cardiac complication, and another one had hepatic AVM, one patient complained of intractable migraine without pulmonary or cerebral AVMs (Table 5).

4.1.2 Methods

4.1.2.1 Paper I

The literature has been searched for in Pub-Med, using the following keywords: Epistaxis, epistaxis AND grading system, epistaxis AND classification, epistaxis AND Osler disease, epistaxis AND hereditary haemorrhagic teleangiectasia.

A questionnaire with five questions, concerning the characteristics of an epistaxis grading system (Appendix 2), was sent by e-mail to 22 international medical professionals, who have published papers in the field of rhinology or HHT. The questionnaire was sent to experts in the following countries: Denmark, France, Germany, Iraq, Italy, Japan, Norway, Spain, UK, and USA. One reminder was sent to those experts who had not replied within four weeks.

Comparisons were made between the existing systems and experts' opinions. In case of discrepancy between the experts' opinion and the existing grading systems, the decision was made in favor of the experts' opinion. In case of discrepancy among experts' opinions also, we chose the criterion, which we believed that was more appropriate.

Using this as basis, the final version of the aimed grading system was shaped by own experience.

4.1.2.2 Paper II

The grade of epistaxis was obtained by recording the intensity, the frequency and the amount of blood transfusion during the period of the last four weeks before the date of consultation or the telephone interview (Table 2). The grading had been converted into a single scale by multiplying the intensity (I) by the frequency (F), adding blood transfusion (T). Zero had been referred as “No bleeding”, 1-5 as “Mild”, 6-10 as “Moderate”, 11-15 as “Severe”, 16 and more as “Intractable”.

The grading of epistaxis of the untreated group was obtained by telephone interview.

All patients were genetically tested for *ENG* and *ALK1* gene mutation. All patients were asked about the age of onset of spontaneous recurrent epistaxis.

Statistical analysis: Association of epistaxis grade with age, gender, gene mutation, and age of onset of epistaxis was calculated using the contingency of chi-square tables and Fisher’s exact test. Spearman’s rank correlation was performed between age of onset of epistaxis and the grade of epistaxis. A power analysis was performed for the outcome gender and the grades of epistaxis, and between the outcome age of the patients and the grades of epistaxis.

In addition, the association of epistaxis frequency (F) and epistaxis severity (I) with age, gender, gene mutation, and age of onset of epistaxis was also calculated using the contingency of chi-square tables (these data was not published in paper II).

4.1.2.3 Paper III

Demographic and HHT disease-related information

The questionnaire registered demographic and HHT related information. The demographic variables included age, level of education, marital status, and work status.

HHT related information was based on the Symptom-specific questionnaire in HHT patients (SFB-HHT) (91) (Appendix4). This questionnaire contained items like: duration since the start of the first manifestation, age of onset, mutation type and Curaçao criteria. In addition this questionnaire contained items about the nosebleeds like: if nose bleedings had more impact on daily life than other manifestations; nose bleedings impact on participation in daily working and other social life; time used on nose care per day, and intensity and frequency of epistaxis. Discomfort due to treatment of nose bleedings and the number of treatments in local anesthesia last year were also registered. Patients were asked if they had pain in relation to HHT, with response options: yes / no. In addition, they had been asked (if the answer was yes) what kind of pain they had. The kinds of pain reported were: headache, pain in the abdomen and nose or nasal region, pain related to treatment and general pain in the body (unpublished data).

Quality of life

QoL was assessed in three levels:

1. Overall QoL using Cantril's Self-Anchoring Ladder (CL), which is a self-administered questionnaire with one question: "How is your life?" The response alternatives are 0 - 10 (0 = worst QoL, 10 = best QoL).
2. Short Form 36 (SF-36) (95;96), which measures eight dimensions: physical functioning (PF), role limitation due to physical health problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). Physical component scale (PCS) and Mental component scale (MCS) are constructed on the basis of the items

from these dimensions. VT, SF, RE, and MH contribute to MCS, while PF, RP, BP, and GH do so for PCS.

According to standard (SF-36) scoring, all scores were transformed into a 0 (worst) to 100 (best) scales. Score <40% was regarded as poor QoL (97).

3. Disease-specific quality of life questionnaire in HHT patients (SFB-HHT-Q, Appendix 4): using the following question: "To which level does the disease impact your Quality of life?" The answer alternatives are from 1 which corresponds to ''no impact on QoL'' and to 10 which corresponds to ''the worst possible QoL''. A cut-off score was chosen at 6 or lower (1–6 score corresponds to no or small impact on QoL)

Higher score of SF-36 and (CL) reflect better QoL, while higher SFB-HHT score indicating that the disease has more impact on the QoL.

Statistical analyses: Categorical variables were analyzed with chi-square tests. Quality of life measures were analyzed using independent sample T-test.

Hierarchical multiple regression analyses were used to examine possible associations between demographic and HHT disease related variables as independent variables, and different QoL scores as dependent variables.

4.1.2.4 Paper IV

To evaluate the effect of the intranasal bevacizumab therapy, the grades of epistaxis were recorded by using IFT grading and the ESS system. The grades were recorded immediately before the treatment by direct interview and monthly after the treatment by telephone interviews. In addition, hemoglobin levels were measured immediately before and monthly after the treatment. Quality of life was evaluated before and four weeks after the procedure by health related quality of life questionnaire (HR-QoL) SF-36. In addition, overall QoL was

evaluated by Cantril`s Self-Anchoring Ladder (CL) and the disease specific QoL was evaluated by SFB-HHT-Q. The patients themselves filled these questionnaires.

The injection procedure was done in local anesthesia with light sedation in 7 out of the 8 patients. A total dose of 100 mg bevacizumab was injected submucosally. Each of the following areas was injected with 0.5 ml bevacizumab on each side:

1. The sphenopalatine area.
2. Upper part of bony septum.
3. Upper part of the lateral nasal wall.
4. The anterior floor of the nose.

These four areas correspond to the points of entry of the main arteries responsible for the blood supply of the nasal mucosa, which are: the sphenopalatine artery, the anterior ethmoid artery, the posterior ethmoid artery and the greater palatine artery (Figure 1 in paper IV).

The procedure was endoscopically assisted, using 0° and/or 30° rigid nasal fibro-optic scope. No cauterizations or laser photocoagulation were done during or after the procedure.

Statistical measures:

Paired sample t-test was used to compare the difference between pre- and post- treatment parameters. SPSS version 18 was used for the statistical calculation.

Chapter 5:

5.1 Results

5.1.1 Paper I

In the literature, four different grading systems have been applied for the grading of HHT associated epistaxis (Appendix 1).

The first one (78) depends on a disease-specific questionnaire assessing the severity and frequency of bleeding using a visual analogue scale and information regarding other treatments such as blood transfusion. In addition the QoL has been taken into consideration. The epistaxis was graded into: mild, moderate and severe. The second grading system categorized the grade of HHT associated epistaxis into mild, moderate and severe (6;87). It used the frequency and duration of bleeding as one item, and the need of blood transfusion as another item and merged these two items in one scale (single multi-item scale). A forth grade (intractable bleeding) has sometimes been used in this system (87). The third system was a two scales system in which the severity (intensity) of bleedings was taken as one scale, graded into three grades from 1 to 3 while frequency of bleeding was taken as another scale, graded into other three grades from 1 to 3 (82;85). The fourth system graded the epistaxis according to the need of blood transfusion, the frequency and the duration of bleeding episodes (98).

The response rate of the questionnaire from the experts was 45%. Half of the experts preferred a “single multi-item scale”, while the others preferred more than one scale. Sixty percent chose the absolute scale. Seventy percent answered that blood transfusion is an important parameter. All of them (100%) wanted the system to be easy to understand for the patient. Ninety percent wanted the system to focus on a definite time period, while 10% wanted it to focus on a single bleeding episode.

5.1.2 Paper II

Ninety-eight patients were included. The female : male ratio in the total group was 1.9:1. The age ranged between 10-90 years (mean: 51, SD =16). Fifty-seven percent of the patients had mild epistaxis, 33% moderate, 5% severe, 2% intractable, and 3% did not complain of epistaxis at the time of running this study. Forty-four percent of females suffered moderate, severe or intractable grade of epistaxis, in contrast to 32% of males. This difference was not statistically significant. Considering 10% difference between females and males, for a power of 80% with a female : male ratio of 2, the total sample needed would be 883 patients (294 males and 589 females). There were no statistically significant associations between the frequency (F) or the intensity (I) of the epistaxis and the gender (unpublished data).

Epistaxis in patients less than 30 years old was mild to moderate. Severe grade of epistaxis was seen only after the age of 30 years and intractable epistaxis was not observed before the age of 50 years. The percentages of more severe grades of epistaxis increased slightly with age. None of the patients under the age of 30 years reported a daily bleeding. Daily epistaxis was reported only among patients over 30 years old. Similarly, high intensities of epistaxis (I >2) were seen only after the age of 20 years (unpublished data). These findings suggested that HHT associated epistaxis is progressive with age; however, none of these findings were statistically significant.

Six patients showed neither *ALK1* nor *ENG* mutation. Fifty-five patients had *ALK1* mutation and 37 patients had *ENG* mutation. All the non-*ALK1*, non-*ENG* suffered mild grades of epistaxis. Intractable epistaxis was seen only in the *ENG* mutation group (2 patients). Four of the five patients who suffered severe grade of epistaxis, carried *ENG* mutation. There was no statistically significant difference in the grade, frequency or intensity of epistaxis between *ENG* and *ALK1* subgroups. When comparing the grade of epistaxis in the *ALK1* subgroup with the *non ENG, non ALK1* subgroup, and the *ENG* subgroup with the *non ENG, non ALK1* subgroup separately, a statistically significant difference was found: patients within the *non*

ENG, non ALK1 group showed significant lower epistaxis grades when compared to patients with HHT1 or HHT2 (P=0.04).

Eight of the 98 patients were not sure about the age of onset of epistaxis. The age of onset of epistaxis ranged from 1- 52 years with a mean of 15.7 (SD =14). In 56% of the patients the onset of epistaxis occurred by or before the age of 10 years, and in 77% the onset was by or before the age of 20 years. The latest onset of spontaneous epistaxis was at the age of 52 years.

The two patients with intractable grades of epistaxis started epistaxis before the age of 10 years and both of them carried *ENG* mutation. Four of the five patients who suffered severe grades of epistaxis started epistaxis by or before the age of 20 years and all the four carried *ENG* mutation. One of the five patients with severe grade of epistaxis started epistaxis late (by the age of 50 years), and this patient was the only one in the severe grade group who carried *ALK1* mutation. There was no statistically significant correlation between the age of onset groups of epistaxis and the grade, frequency or intensity of epistaxis. However, 32/35 (91%) of the HHT1 subgroup and 32/49 (65%) of the HHT2 subgroup had age of onset by or before the age of 20 years. This difference was statistically significant (P=0.01, unpublished data).

The treated group consisted of 51 patients (53%). The distributions of the epistaxis grade, epistaxis frequency (F), and epistaxis intensity (I) in the treated and untreated groups were quite similar and there was no statistically significant difference.

5.1.3 Paper III

Sixty-six patients were included, 39 women and 27 men.

Demographics and HHT/disease-related variables

No significant differences were found between the HHT group and the normative sample on any of the demographic variables. All the responders met the clinical criteria for HHT based

on the Curaçao criteria and/or had an *ENG* or *ALK1* mutation. Six responders met the clinical criteria for HHT only. Mean age of onset of epistaxis was 15.4 years (SD = 16.2), while the mean duration of the disease was 14.6 years (SD = 15.0).

All patients reported frequent nose bleeds which affect their participation in employment more than all other arenas of their everyday lives. While some responders defined their nosebleeds as excessive, others described theirs as little or moderate. However, all responders reported devoting time on a daily basis to nose-care due to bleeding. Pain and discomfort, due to the nose bleeds and/or laser treatments or nose packing, was reported. Most of the respondents reported having been treated once or more times with local anesthesia during the previous year.

Overall Quality of life

Seventy-seven percent of the patients reported high level of overall QoL based on the cut-off score of 6. A higher number of Curaçao criteria and pain showed differences to a significant level, with $P<0.001$ for both variables.

Health-related quality of life (SF-36)

Mean score: the mean scores of SF-36 domains ranged from 50.2 to 80.5 with MCS (50.5 ±9.3) and PCS (44.3 ±10.4).

Comparison with the normative sample: When comparing the HHT group with normative sample, the mean scores for all scales of the SF-36, except for BP, were significantly lower in the HHT group including MCS and PCS.

Demographic variables: the mean scores of PF and PCS were significantly higher among those having higher levels of education. PF, BP, GH, RE, and PCS showed lower scores to a significant level for unemployed patients. There were no significant differences between genders in SF-36, except for BP.

HHT-disease-related variables: significant differences in HR-QoL were found in time used on nose care, intensity of epistaxis, Curaçao criteria (number of manifestations), and discomfort due to epistaxis. Frequency of nose bleedings was found to be significantly associated with poorer QoL in RE. Time since diagnosis showed a significant association with poorer PCS. No significant differences were found between *ALK1* and *ENG* mutation groups.

Having HHT related pain was associated with significantly poorer level of all aspects of HR-QoL. On the other hand, comparing the HR-QoL of the 51 patients who did not report having HHT related pain, with the normative sample, showed that this patient group has a significantly better BP than normative sample, but poorer RP, GH, VT, RE and MCS (unpublished data).

Disease specific QoL, SFB-HHT –Q

Fifty-eight percent of the included patients reported that disease-related QoL was negatively associated with HHT. Among HHT disease-related variables, more time used on nose-care, intensity of nosebleeds, and pain were associated with poorer disease-related QoL as measured by SFB-HHT-Q.

Multivariable hierarchical linear regression analyses

HHT disease related variables were significantly associated with overall quality of life (CL), and explained 30% of the variance in overall quality of life. Among the HHT disease related variables, Curaçao criteria had the strongest unique contribution.

Demographic and HHT disease-related variables were both associated with MCS significantly. HHT disease-related variables explained 16% of the variance in MCS, with pain and being tired as the factors making statistical significant unique. Altogether, the multivariable hierarchical model explained 35% of the variance in MCS.

The multivariable hierarchical model explained 68% of the variance in PCS. The HHT disease-related variables contributed significantly to the final steps with 52% of the variance of PCS. Only HHT disease-related variables contributed significantly to the final model. Pain had the strongest associations with physical quality of life.

According to the disease specific quality of life (SFB-HHT-Q), HHT disease related variables contributed significantly to the final model. The multivariable hierarchical model explained 37% of the variance in disease specific quality of life, and time used to nose care per day had the strongest association with SFB-HHT-Q.

5.1.4 Paper IV

The effectiveness of the intra nasal bevacizumab injection was evaluated firstly four weeks after the first treatment. Three of the eight patients did not respond to the bevacizumab injection and two of these three received additional injections, of the same dose, four weeks after the first dose.

The mean time from the first bevacizumab treatment until the last epistaxis severity evaluation was 9.5 weeks (range = 8 – 12, SD = 1.4). The mean pre-therapy IFT epistaxis grade was 14.3 (range = 7 – 25, SD = 7.0). The mean post-therapy IFT epistaxis grade was 3.5 (range = 2 – 7, SD = 1.6). The difference between pretreatment and posttreatment IFT grading was statistically significant (P = 0.007). The mean pre-therapy intensity (I) was 5.1 (range = 3 – 7, SD = 1.3). The mean post-therapy intensity (I) was 1.9 (range = 1 – 3, SD = 1). This difference was significant (P = 0.02). The mean pre-therapy frequency (F) was 4.9 (range = 4 – 6, SD = 0.6). The mean post-therapy frequency (F) was 3.1 (range = 1 – 6, SD = 1.5). This difference was significant (P = 0.01) (Table 7).

The mean pretreatment ESS was 6.0 (range = 4.70 – 8.25, SD = 1.21). Post-therapy ESS average was 2.82 (range =1.96 – 4.98, SD = 0.92). This difference in ESS was statistically significant (P = 0.001).

The mean pretreatment hemoglobin level was 10.6 g/dl (range 8.4 – 13.2, SD = 1.6). The mean posttreatment hemoglobin level was 13 g/dl (range 8.0 – 17.1, SD = 2.8), (P = 0.01). None of the patients received blood transfusion after the treatment. No changes had been done to the dose of iron supplement therapy after the treatment except for patient number 6, in whom the family doctor discontinued the iron supplement four weeks after the treatment because of the dramatic and rapid improvement in the hemoglobin level.

The effect of the therapy on HR-QoL, measured by SF-36, showed improvements in all SF-36 dimensions except bodily pain (BP). These improvements were not statistically significant. As well, there was an improvement in the mean of overall QoL score and the disease specific QoL. These improvements did not however reach statistical significance.

Chapter 6

6.1 Discussion:

6.1.1 Purpose of the work

In this work HHT associated epistaxis has been studied from different aspects. Paper I focused on grading systems of HHT associated epistaxis. We discussed, in this paper, the importance of having a common internationally accepted grading system, and assessed the different systems that had been used at the time of conducting the study. Finally, the IFT grading was designed as a proposal for an internationally accepted system. In paper II, the grades of HHT associated epistaxis in the Norwegian population was described from diverse aspects using the IFT grading system proposed in paper I. It is the first work that studies the HHT associated epistaxis in Norway and may serve as a base line for further studies. It added more knowledge about the natural history of HHT associated epistaxis generally and made it possible to compare the HHT population in Norway with HHT population in other countries. The ESS grading system, which was proposed by Hoag et al. (84) for the International HHT foundation in 2010, has been discussed in detail in this paper.

Paper III described the impact of HHT manifestations generally and HHT associated epistaxis particularly on different levels and aspects of QoL in the Norwegian HHT population.

In paper IV, we discussed our experiences with bevacizumab as a new treatment option for HHT and presented the application of the IFT grading and the ESS systems.

6.1.2 Grading of HHT associated epistaxis.

Paper I depended on three sources of knowledge. The first one was the main four grading systems from the literature, which were in use at the time of running the study; the second

source was medical experts' opinions; and the third source was our experience in treating and follow up HHT patients at the Department of Otorhinolaryngology, Head and Neck Surgery in Oslo University Hospital / Rikshospitalet. The four grading systems were evaluated in five aspects:

1. The type of grading scale.
2. Whether they were *relative* (without end point) or *absolute* scales (take at least one end point, as zero, in consideration).
3. Whether blood transfusion was taken as a factor in the grading.
4. Whether a definite time period was included as a factor in the definition of the scale.
5. Whether the grading system was easy to understand for the patients.

Experts' opinions about these five aspects were collected using a questionnaire. Five questions corresponding to these five aspects were sent to 22 international medical experts, who have published results in rhinology or HHT. Ten of the experts responded. This response rate of 45% was low. A possible explanation of the low response rate is that the questionnaire was sent by e-mail and in this way it is impossible to be sure that all the e-mails have been received. Telephone call might be a better way to collect the experts' opinions. Nevertheless, the low response rate might be a cause of bias.

By comparing the existing systems and the experts' opinions we found that all the existing systems are easy to understand and to use by the patients. The exception might be the system used by Lund et al (78) which need an additional QoL questionnaire. Similarly all the asked experts wanted the system to be easy to understand for the patients. Therefore, we concluded that the aimed system should be easy to comprehend for the patients.

The existing systems either do not focus on a definite observation period or the observation period is not a fixed period but varied (week, day or lifetime) from one grade to the other in the same system. On the contrary, 90% of the experts wanted the system to focus on a definite

time period. In addition, having a definite time period of observation makes the system more appropriate to be used both in cross sectional and longitudinal follow up studies. Therefore, we concluded that the aimed system should focus on a definite time period of observation. We chose a four weeks period of observation, considering the chronicity of HHT and the known fluctuating character in severity of HHT associated epistaxis. A shorter period may not be representative of the actual epistaxis severity, and a longer period will increase the recall bias, as the patient usually will not remember how the situation was for more than four weeks ago.

Although HHT patients may need blood transfusion due to GI tract bleeding and not only epistaxis, blood transfusion is taken as a factor in three of the four existing grading systems. Seventy percent of the experts regarded the need of blood transfusion as an important parameter in assessing the severity of HHT associated epistaxis. For this reason, we found it necessary for the aimed grading system to include the need of blood transfusion as a parameter.

There was no clear tendency among experts' opinions or among the existing systems towards a "single multi-item scale" or "multi-scale system". Two of the four systems are multi-scale systems, while the other two are single multi-item scale (Appendix 1). Similarly halve the experts preferred a "single multi-item scale", while the other halve preferred more than one scale. On the other hand, at least in two of the four systems the frequency and the intensity (or severity) of the bleeding are used as two separate parameters. In one system the frequency and the duration of the bleeding are used as two separate parameters. As mentioned above, we found the need of blood transfusion necessary to be encountered in the aimed system as a parameter also. Therefore the aimed system should consist of multiple scales, as the frequency, intensity and blood transfusion. We chose the intensity rather than the duration because two of the existing systems use intensity and only one uses the duration. However, since halve the experts wanted a single scale system, we concluded that the aimed system

should be easy to be converted to a single scale system. We believe that both the "multi-scale" and "single-scale" systems have advantages. The multi-scale system gives the possibility to follow changes in the frequency and the intensity of the epistaxis separately, and the single-scale system (grading the epistaxis as mild, moderate, severe…etc.), is also desired especially in the daily clinical work.

All the existing systems are relative systems without an end point. On the other hand there was only small tendency among the experts toward absolute scale (60%). Nevertheless, it is known that HHT associated epistaxis is a swinging and variable symptom. Therefore, HHT patients who do not complain of epistaxis, as for instance during the period after treatment, could not be included in the grading system without having the zero end point. Thus, we found it essential that the aimed system is an absolute scale with a zero end point.

According to this, a grading system has been designed as a proposal for an aimed system (Table 2). It is a multi-scale grading system, composed of three scales, which are: epistaxis intensity (I), epistaxis frequency (F) and the number of blood transfusions (F). This will give the opportunity to score the HHT patients according to their epistaxis frequency, epistaxis intensity, or the need of blood transfusion independently. In addition, the system can be converted to a single scale system which grades the epistaxis to: no bleeding, mild, moderate, severe, and intractable grades (as shown in paper II) by multiplying the digits corresponding to the frequency by the intensity and adding the blood transfusion. It focuses on a definite time period of observation, four weeks retrospectively. There is one absolute end point of the scale, which is zero. It is easy to understand for the patient when converted into five questions (Appendix 3).

The grading score proposed by Hoag et al. (Table 4) for the International HHT foundation was discussed in paper II (84). This is an absolute and single multi-item scale, which includes the need of blood transfusions as a risk factor and is easy to understand for the patient. This

system does not focus on a definite time period. It scores the severity of HHT associated epistaxis according to epistaxis frequency, duration, intensity, need for transfusion, anemia, and aggressiveness of treatment required. The coefficient factors of these risk factors were calculated based on opinions of HHT patients. Eighty-nine percent of the patients in the Hoag study were from North America. Comparing the score with the invasiveness of treatment performed the external validation. The internal validation was performed through bootstrapping methods. It is hard to accept that a scoring system that predominantly was based on opinions of North American HHT patients would be generally suitable for all other nations. The opinions of HHT patients will probably be different, especially in respect to the factors as the need for blood transfusion, anemia and aggressiveness of treatment. These factors depend on the availability of professional health care providers and therefore depend on the health care system of the country. In addition, the definition of anemia as risk factor was not clarified. It was based on patients' opinion on anemia, not on the hemoglobin level. Anemia is generally a complex issue. For the calculation of a coefficient factor for anemia it would be natural to use data on the hemoglobin and iron levels. On the other hand, we appreciate the study from Hoag and others, because it provides, for the first time, coefficient factors for different epistaxis related factors.

6.1.3 HHT in the Norwegian population.

This was the first study of HHT in the Norwegian population. It focused on two main aspects:

1. The grading of HHT associated epistaxis in relation to different risk factors.
2. The impact of HHT on different aspects of QoL.

6.1.3.1 Grading of HHT associated epistaxis in the Norwegian population.

Paper II described the natural history of HHT associated epistaxis in the Norwegian population, in a cross sectional approach. The study focused on the grade of epistaxis in relation to risk factors like gender, age, gene mutation type and age of onset of epistaxis. The results were compared with the results of similar studies from other countries. The result of this cross sectional study could be used as a base for a future longitudinal study, concerning the changes in the HHT associated epistaxis with time.

Because of the small sample size, although comparable to other published studies, it was important to describe and discuss all the observations even if they did not achieve statistically significance.

Gender:

It was observed more females than males in our study with a ratio of 1.9:1. This is comparable to other HHT populations in Europe and USA (1;3;11;29;55;56), but this contradicts to some extent the fact that HHT is an autosomal dominant (non-sex linked) disease, and the expected female : male ratio should be 1:1, or at least 1.1:1 since the female: male ratio in the whole Norwegian population is 1.1:1 (99). This deviation in the female : male ratio from the expected 1:1 has been mentioned in other studies concerning HHT associated epistaxis (1;46;88;98) and was statistically not significant in two of them (1;98), and significant in one study (88). A possible explanation of this deviation of the female: male ratio is the fact that females are usually more oriented to self health care than males, and seek health care earlier than males (100;101), and this makes females over represented in such studies compared to males. A possible explanation was that females are more severely affected by the disease than males, because of the chronic blood loss due menstruation, which can lead to more obvious symptoms and early diagnosis. Another possible explanation is the hormonal factor. It has been mentioned that females generally suffers milder HHT related bleeding during pregnancy

and during the use of estrogen-containing contraceptives, and the symptoms worsens after menopause (102). This can also explain the tendency of more severe grade of HHT associated epistaxis among females than in males (although statistically not significant in our study). Nevertheless, deviation of the female: male ratio in our study and previous studies may represent a recruitment bias.

Age:

Severe grade of epistaxis was found only among patients who were 30 years old or more and intractable grade could be found only among patients who were 50 years old and more. This finding, yet not statistically significant, gave the impression that the HHT associated epistaxis may be progressive with age. Similar observation has also been mentioned in other reports and was found to be not significant in two studies (1;55), and significant in other studies (3;11;88;89). This may be due to the assumption that HHT itself is progressive with age or aging processes, like arteriosclerosis, worsen the severity of epistaxis. However, it is a clinical experience that HHT associated epistaxis in elderly patients often is more severe and more difficult to treat.

Gene mutation:

Many studies, concerning the genotype-phenotype correlations of the HHT, have shown significantly higher prevalence of PAVMs (9;10;15;29-31;66;103), and CAVMs (9;15;31;66) in HHT1 than HHT2 subgroups of the disease. In addition, HHT1 is associated with larger PAVM than HHT2 (9;30). On the other hand hepatic involvements are more common in HHT2 than HHT1 subgroups (9;15;31). However, there is no clear difference in the prevalence of GI bleeding between the two subgroups of the disease (9;15;29;31;103).

Four of the five patients with severe grade of epistaxis in our study, and both of the patients with intractable grade were carrying *ENG* mutation. This observation, although not statistically significant, gave impression that there is a trend of the HHT1 to be associated with more severe grades of epistaxis than HHT2. Kjeldsen et al. (103) reported quite similar results in their 73 patient sample. *Non ENG, non ALK1* carrier patients had a significantly lower grade of epistaxis than *ENG* or *ALK1* carrier patients in our study. This observation has not been mentioned in the other studies. This finding might be of interest for future research.

Age of onset:

Seventy-seven percent of the patients started epistaxis by or before the age of 20 years and 56% by or before the age of 10 years. This was consistent with the general agreement that HHT associated epistaxis starts early in life and usually is the first symptom. Assar et al. found that 54% of their HHT patients started epistaxis by or before the age of 10 years and 90% before the age of 21 years (1). Forty-five percent of the patients in the Folz et al. material started epistaxis in childhood age, and epistaxis was the first manifestation of HHT in 93% of the patients (3). More than one-half of the HHT patients in the study from Reilly et al., started epistaxis during the first decade of life (56). Plauchu et al. described in a material of 324 patients, that the onset of epistaxis was before the age of 20 years in 50% of the patients and before the age of 45 years in 90% (11). There was no statistically significant association between the age of onset of epistaxis and its severity in our study. On the other hand, considering the gene mutation, we found that HHT1 patients started epistaxis in significantly earlier age than HHT2 patients (unpublished results), which is in line with many previous studies (9;10;29;31;103).

Role of treatment:

There was no statistically significant difference in the grade of epistaxis between the treated and untreated groups. The untreated group included some patients who had been treated for epistaxis longer than two years before enrollment. Therefore, conclusions regarding the effect of the treatment on the natural history of HHT associated epistaxis would not be reliable from this study. Actually the term "natural history" should be referred only to those patients, who have not been treated for epistaxis at all throughout all their life. Such patients would represent mostly patients with very mild grade of epistaxis or no epistaxis at all, since it is expected that patients with higher grades of epistaxis have been treated previously. Including only patients who have not undergone treatment at all will lead firstly to a selective bias, and secondly to a much smaller sample size with a consequence of low statistical power.

6.1.3.2 The associations between HHT and Quality of life in the Norwegian population.

General consideration:

The main findings of this study were that several HHT-disease related variables showed significant associations with all three levels of QoL, overall QoL (CL), mental HR-QoL (MCS), and physical HR-QoL (PCS) as well as disease-specific QoL (SFB-HHT-Q). HHT disease-related variables also explained more of the variance than demographic variables in all types of QoL except for the MCS.

Gender:

The difference in QoL between genders in our sample was that females had worse BP than males. Pasculli et al. found lower level PF, RP, RE, and SF in addition to BP, as well as lower levels on the PCS in women compared to men (79).

Associations between HHT-related variables and QoL:

Epistaxis:

The observations were that frequency and intensity of epistaxis are associated with reduced HR-QoL. However, the associations vary to different degrees with respect to different dimensions as Physical functioning (PF), Role physical (RP), Social functioning (SF), Role emotional (RE) and the physical component scale PCS. In addition, the higher level of intensity of nosebleeds, as well as time used to nose care, showed reduced disease-related QoL. This conclusion, the higher severity the poorer QoL, make sense, as well as they are in line with former studies (77;79;90;91).

Gene mutation:

There were no significant differences in any QoL level between HHT1 and HHT2 in our material. This was in concordance with our results in paper II in which no significant differences in the epistaxis severity could be found between *ENG* and *ALK1* carriers. This agreed also with Kjeldsen et al. study from Denmark (103). Pfister and co-workers surveyed 24 patients with identifiable mutation in either the *ALK1* or *ENG* genes in Germany and found lower QoL due to PF, RP, BP, GH as well as the PCS, in patients with identifiable mutation in the *ENG* gene (104). The higher statistical power in our study, with 60 patients with an identifiable mutation, compared with 24 patients in Pfister et al. study, makes our results more statistically reliable.

Number of manifestations:

Fulfilling four Curaçao criteria was associated with lower score on GH, VT and MH of the HR-QoL. In addition, having four Curaçao criteria was associated with lower overall QoL

(CL) score. Fulfilling four Curaçao criteria represents a higher severity of the disease, and this may be a logical correlation.

Pain:

Experiencing HHT related pain was the only variable that made a statistically significant contribution to all levels of QoL in the multiple regression analysis. Additionally, all aspects of HR-QoL among patients with HHT related pain were poorer than patients without HHT related pain. On the other hand, the 51 patients who did not report having HHT related pain, showed significantly better BP, but poorer RP, GH, VT, RE and MCS than normative sample (unpublished data). Therefore, although pain is not a well recognized symptom of HHT, it has a strong negative impact on QoL when present.

This makes pain an important aspect in considering new treatment methods of epistaxis. Painful methods may cause negative impact on the QoL, in spite of being objectively effective.

Comparison to other normative samples:

The level of HR-QoL observed in patients with HHT could be compared to Norwegian normative sample and samples from other studies. Lower level on all scales but BP in SF-36 compared to the normative sample is in line with the findings in earlier studies (79;90).

Comparison to other samples:

Compared to the Italian HHT sample in the study by Pasculli et al., our patients had significant higher mean score on several dimensions, as well as the MCS (79). We observed a significantly better score in disease-related QoL in our HHT sample than reported in the

German sample (91). It is difficult to explain why Norwegian patients with HHT report higher HR-QoL and disease-specific QoL than responders from other countries.

The level of CL in our sample of individuals with HHT was found to be similar to CL level of patients with other chronic diseases in our database (not published).

Objective vs. subjective QoL:

Approximately 77% of the HHT patients included in this study, reported a high level of overall QoL. On the other hand, taking this particular disease into account, 58% stated that the HHT had negative impact on their QoL, and they had poorer HR-QoL than the age- and gender-adjusted normative sample. The discrepancy between what they express about their overall QoL, ‘‘their subjective telling’’ and what they report in the HR-QoL, and the reduced QoL compared to normative sample, ‘‘the objective findings’’ may be due to their particular situation, and their use of coping strategies like acceptance and positive reinterpretation and growth.

These findings underscore that the perceptions of QoL are of subjective nature, and that targeting non-clinical factors like coping, seems to be positively associated with QoL. In a systematic review of the literature on QoL in rare genetic conditions Cohen and Biesecker found strong correlations between QoL and psychosocial factors beyond the physical manifestations of the disease like coping, illness perceptions and self-esteem, demonstrating the importance of such factors in determining an individual’s QoL (105). They concluded that the individual’s adaption due to living with genetic conditions generate a gradually attain to restore optimal QoL. Our findings are in line with this. Even if our respondents report experiencing a relatively strong impact of disease-related QoL as well as poorer health-related QoL than the normative sample, it seems likely that they have adapted to their situation evidenced by their reports of good overall QoL.

6.1.3.3 Statistical power and the representativeness of the sample:

The small samples size in paper II and III, due to the rarity of the disease and the known problem of underdiagnosis, caused a statistical power deficiency. We tried to improve the power in paper II by fusing some of the subgroups in bigger groups as done by fusing the "no bleeding" and "mild" in one group and the "moderate", "severe" and "intractable" in another group and fusing the age groups to "<40 years", "40-59 years" and "≥60 years".

Two power analyses have been performed in paper II. The first one was for the association of the grade of epistaxis and the gender, and the second one was for the association of grade of epistaxis and the age of the patient at the time of running the study. We chose these to aspects (age and gender) for the power analyses because these aspects showed the largest differences (although not significant). The power analyses showed that the sample size needed to get an acceptable statistical power regarding association of the grade of epistaxis and gender would be 883 patients and regarding the grade of epistaxis and the age would be 1032 patients. This is almost the total expected number of the HHT patients in Norway, which is expected to be about 625 – 1000 patients, considering a prevalence of HHT of 1/5000-8000 (52-54) and the total population in Norway of about 5 million (99). So, to get an acceptable statistical power, we had to include all HHT patients in Norway including undiagnosed patients, which is practically impossible in the national setting. Keeping in mind that the sample size needed regarding the other aspects like: age of onset and gene mutations is expected to be even higher, since the differences in these aspects were less.

The HHT team at Oslo University Hospital-Rikshospitalet represents the only "HHT center of excellence" in Norway. Most patients with clinical suspicion of HHT are referred to Rikshospitalet from all over the country, and all patients with definite HHT diagnosis (3 or 4

Curacao criteria), and patients with suspected HHT diagnosis (1 or 2 criteria) with positive gene test for *ALK1, ENG* or *SMAD4*, and asymptomatic first degree relatives with a positive *ENG* or *ALK1* gene mutation test, were registered in this data-base. The HHT data-base in Rikshospitalet can be considered as a representative sample of HHT population in Norway. At the time of running the study of paper II, there were 160 patients registered in the database, of which 109 patients were with definite HHT diagnosis (3 or 4 Curacao criteria). Ninety-eight (90%) of the 109 patients were included in paper II while 11 patients (10%) could not be followed up mostly because of communication difficulties. Therefore, we assume that the sample in paper II was representative for the HHT population in Norway at the time of running the study. Patients with only two diagnostic criteria with a positive gene test were not included in paper II. Enrolling these patients would enlarge the sample size (anyway not to the level of acceptable statistical power), but this would be on the expense of the possibility of including some patients who did not yet complete the clinical picture of the disease, and hence not representing the complete "natural history" of the disease.

Power analysis has not been done in paper III. However, in spite of an even smaller sample size than paper II, we expect that the large control group of 990 persons lead to a better statistical power regarding HR-QoL.

The lower response rate in paper III might be due to the burdens and limitations of everyday life experienced by HHT affected patients, but it might also be interpreted as an expression of their experiences of having a good life despite HHT. We had no possibility to do attrition analysis. On the other hand, the sample size in paper III was comparable to earlier studies in the area regarding HHT and QoL (79;90;91;104) and we suggest that our findings are representative for Norwegian HHT patients in general.

However, we do not know the exact number of patients with HHT in Norway who have not been registered in the database at Rikshospitalet.

6.1.4 Anti-VEGF in treating HHT associated epistaxis:

A wide variety of treatment options has been used for treating HHT associated epistaxis (78) (Table 3). All of these treatment options have some limitations and complications, and none of these options fit all of the patients. Therefore, new options are demanded. The new options should consider the other HHT associated morbidity, like pulmonary, hepatic, gastrointestinal and nervous system involvement.

Understanding the genetic and molecular background of HHT opened the door for new treatment options. The high serum level of VEGF (51;106), identifies VEGF as a possible therapeutic target in HHT.

Bevacizumab is a recombinant, humanized, monoclonal antibody that binds to and inhibits the biological activity of VEGF, and hence reduces endothelial cell proliferation and angiogenesis (93;107).

Intravenously administered bevacizumab has been used in treating HHT associated anemia secondary to GI-bleeding and epistaxis, and heart failure secondary to hepatic AVM (74;93;108-112).

Several groups have proposed intranasal administration of bevacizumab as a possible new treatment modality in HHT associated epistaxis. Davidson et al. published the first case report of using intranasal bevacizumab injection and spray in local anesthesia for treating HHT associated epistaxis, and concluded that intanasal bevacizumab could be a promising new treatment of HHT associated epistaxis (113). Simonds et al. treated 10 patients with KTP laser combined with intranasal injection of bevacizumab, and nine patients with KTP laser alone, and found that the combined therapy significantly decreases the frequency of nosebleed and the need for blood transfusions, and improve QoL measured by work disability and social life

improvements (93). Karnezis et al. recently published their results of treating 32 HHT patients with intranasal bevacizumab, applied as either a topical spray or submucosal injection (114). They reported significant improvement in ESS after this treatment. The injections were done under general anesthesia. Chen et al. found intranasal bevacizumab is safe in treating HHT associated epistaxis (115).

Paper IV describes a standardized intranasal administration of bevacizumab based on the anatomical vasculature of the nasal cavity (Figure 1 in paper IV). Our hypothesis was that injecting bevacizumab in or near the entrance points of the blood supplying vessels, could lead to more effective as well as more equal distribution of the drug to the whole nasal mucosa, thus resulting in improved therapeutic effect. Restricting the injections into four sites will make the procedure more suitable to be done in local anesthesia with light sedation.

Epistaxis grades, hemoglobin levels, and QoL were used to evaluate the effectiveness of the treatment. Both the IFT and ESS epistaxis grading systems were used.

Although the study design is a prospective study, the epistaxis grades were recorded retrospectively regarding the bleeding experience during the last four weeks before the treatment date, and monthly after the treatment date. This might lead to placebo effect, since the patient might report the last four weeks before inclusion as worse in order to be included in the study, and might report the four weeks after the treatment as better period believing that the treatment works and to please the doctor. However, the changes in IFT grades during 2-3 years prior to inclusion into the study (Table 5) do support the value of the actual IFT grade during the four weeks before treatment. In addition, using the hemoglobin level as an objective measure in assessing the effect of the treatment, a significant improvement of the hemoglobin levels was in line with the improvement according in the grading scales.

The QoL was evaluated in three levels as in paper III; 1) Overall QoL measured by Cantril Ladder questionnaire; 2) Health related QoL measured by SF-36 questionnaire; and 3) Disease specific QoL measured by Slotosch questionnaire.

Five of the eight patients showed significant improvement in IFT, ESS and hemoglobin levels after the first treatment, whereas two patients needed two doses before showing a significant effect. One patient showed no improvement at all even after a second treatment.

Both patients with septal perforation (patient nr. 4 and nr.8 in table 5) responded after the first dose. The only patient, who had been operated with septodermoplasy (patient nr.5 in table 5), did not respond to the first treatment dose, but responded after the second dose. We could not find a reason behind the lacking response of patient nr.7. Measuring the plasma level of VEGF may give an explanation in the future.

There was no significant improvement in any of the three QoL levels, four weeks after the treatment.

Several studies have shown that epistaxis has the greatest impact on QoL in HHT patients (79;90;92;104;116-118). However, other variables including duration of illness, and the presence of other HHT manifestations like cerebral, pulmonary, gastrointestinal and hepatic involvement have significant impact on the QoL in HHT patients (79;90;104;117;119). Almost all the eight patients included in paper IV had other HHT complications (Table 5), and were among those who were most badly affected by HHT. In addition, their average QoL values were significantly lower than average of QoL values of the 66 HHT patients included in paper III (Table 6). This might influence the sensitivity of QoL measures for the improvement in epistaxis after the treatment, and a dramatic improvement in QoL was less expected. This may explain the lack of significant improvement in QoL after treatment in our study. On the other hand, generic QoL questionnaires have limited sensitivity, and a more clinically sensitive and responsive instrument for therapeutic evaluation in patients with

epistaxis is missing (117). Simonds et al. (93) used QoL measured by work disability and social life improvements to evaluate the effect of local bevacizumab treatment. Ingrand et al. (117) have newly introduced an epistaxis specific quality of life questionnaire as a complementary tool for treatment evaluation of HHT associated epistaxis.

Only few studies used HR-QoL measured by SF-36 questionnaire to evaluate the effectiveness of different treatment options of HHT associated epistaxis (92;120;121).

A variable individual sensitivity may mirror individual therapeutic resistance to bevacizumab. Therefore, it would be desirable for future studies to evaluate possible measures to predict the individual sensitivity pattern and to monitor the therapeutic response to bevacizumab. Monitoring the serum level of VEGF before and after the treatment with bevacizumab might be the first step in this evaluation.

All the included patients had been previously treated with diode laser, pulsed dye-laser and/or argonplasma coagulation. Although it was not the aim of the study to compare the effectiveness of the previous treatment modalities with the currently described bevacizumab protocol, our impression is that the local therapy with bevacizumab may be of superior effectiveness. In this context, it is worth to mention that a single bevacizumab injection is at the moment more expensive (costs in Norway: 3470 NOK / 100 mg ≈500 EUR) than most of the other treatment modalities mentioned above, and it is unclear yet how often this treatment has to be repeated to gain comparable or better effect than the above mentioned methods. Nevertheless, this has to be further evaluated in the future.

6.1.5 Limitations and difficulties of the study:

1. The response rate of the experts in paper I was low (45%), a higher response rate would be desirable. However the expert's opinion was not the only source of data in paper I,

and we do not expect dramatic changes in the properties of the aimed grading system with higher response rate.

2. The chosen observation period of four weeks in the IFT grading system might be long enough to cause a recall bias (the patient usually remember the last week best). Using a daily nosebleed diary book that the patient fills prospectively might diminish this bias.
3. The IFT grading system still needs evaluation for validation. This can be obtained by test-retest by different operators or by comparing the grading done by the operator with the grading done by the patient, using questionnaire shown in Appendix 3. It would also be of value to evaluate if the grading by IFT system matches with the grading done by other systems as done in paper IV.
4. Paper II was a cross-section study and included patients who have been treated before. Therefore it is not the ideal representative of the natural history of HHT associated epistaxis. The ideal representative of the natural history of HHT associated epistaxis would be a longitudinal prospective study which follows up new HHT diagnosed patients
5. Paper II and III were cross-section studies, and thereby did not allow for causal inferences.
6. The rarity of the disease cause some of the subgroups in paper II and III to be small, which can affect the reliability of the statistical analysis and caused a power deficiency.
7. Gen test for *SMAD4* gene was not done for non *ENG* non *ALK1* patients in paper II and III.
8. Two operators did the grading of epistaxis in paper II and III. This may lead to a cognitive bias (a well known problem in the medical practice). Using the questionnaire shown in Appendix 3 could diminish this bias. In this way the patient him- or herself, not the operator, will grade the epistaxis.

9. The low response rate in paper III (71%) could be due to the burdens and limitations of everyday life experienced by the patients, but it might express their experiences of having a good life despite HHT. We had no possibility to do attrition analysis.
10. Using different grading systems for HHT associated epistaxis, makes comparison of the results in of paper II and III with the results of other studies difficult and may be undependable.

Chapter 7

7.1 Conclusions:

7.1.1 Summary of the main results:

a) A common internationally accepted grading system for HHT associated epistaxis is important both for research purposes and daily clinical routines in this field.

b) There is still no common internationally accepted grading system for HHT associated epistaxis, and the grading system, which was proposed for the International HHT foundation is still not ideal.

c) The rarity of the disease inherently leads usually to small study samples, and thereby, a possible power deficiency.

d) In the Norwegian HHT population:

   1. The incidence of HHT associated epistaxis is 97% in diagnosed patients.
   2. The majority of the patients (77%) started epistaxis by or before the age of 20 years.
   3. The majority of the patients (90%) complained mild to moderate grade of epistaxis.
   4. There was no statistically significant difference in the grade of epistaxis between genders.
   5. There was no statistically significant difference in the grade of epistaxis between HHT1 type and HHT2 type of the disease.
   6. There was a statistical significant difference in the grade of epistaxis between non *ENG*, non *AKL1* carrier and *ENG* or *ALK1* carrier patients.

7. There was no correlation between the age of onset and the grade of epistaxis.
8. HHT1 patients started epistaxis earlier than HHT2 patients.
9. Higher severity of HHT associated epistaxis is significantly associated with lower QoL on all levels, but to different degrees with respect to different dimensions.
10. Although pain is not a well-recognized symptom of HHT, it made a statistical significant contribution to all measures of QoL.
11. There was no significant difference in QoL between HHT1 and HHT2 in the Norwegian population.
12. The only difference in QoL between genders in the Norwegian sample was that females had lower bodily pain (BP) than males.
13. HHT patients have lower HR-QoL than the normative control group.
14. HHT patients in the Norwegian population have better score of QoL in many aspects than HHT patients in the Italian and German populations.

e) Intranasal injection of bevacizumab seems to be an effective treatment for severe and intractable epistaxis graded according to ESS and IFT systems.

7.1.2 Recommendations:

1) More work to design an internationally accepted objective grading system for HHT associated epistaxis is required.
2) Multicenter trials focusing on the natural history of HHT associated epistaxis and the impact of HHT disease generally and HHT associated epistaxis particularly on different aspects of QoL are required to get a larger material with statistically reliable results.

3) Follow up studies concerning the grades of HHT associated epistaxis, QoL in HHT patients and the effect of treatment over long period of time are recommended.
4) More clinical trials are required to find the optimal dose and method of administration of bevacizumab in treating HHT patients.
5) Further studies are required to evaluate possible measures to predict the individual sensitivity pattern and to monitor the therapeutic response to bevacizumab. Monitoring the serum level of VEGF before and after the treatment with bevacizumab might be the first step in this evaluation.

Tables

Table 1: The Curaçao Criteria*(49)

The HHT diagnosis is

Definite if 3 criteria are present,
Possible or suspected if 2 criteria are present, and
Unlikely if fewer than 2 criteria are present

Criteria

1. Epistaxis — spontaneous, recurrent nose bleeds
2. Telangiectases — multiple, at characteristic sites:
   - lips
   - oral cavity
   - fingers
   - nose
3. Visceral lesions such as
   - Gastrointestinal telangiectases (With or without bleeding)
   - Pulmonary AVM
   - Hepatic AVM
   - Cerebral AVM
   - Spinal AVM
4. Family history a first-degree relative with HHT according to these criteria

*All offspring of an individual with HHT are at risk of having the disease since HHT may not manifest until late in life. If there is any concern regarding the presence of physical signs, an experienced physician should be consulted. Coagulation disorders should be excluded. The presence of visceral abnormalities in children should prompt a particularly careful check of other family members. These criteria are likely to be further refined as molecular diagnostic tests become available in the next few years.

Table 2: IFT epistaxis grading scale.

Observation of intensity, frequency and blood transfusion during a period of 4 weeks.					
Intensity of the bleedings (I)		Frequency of the bleedings (F)		Blood transfusion (T)	
0	None	0	None	0	None
1	Slight stains on the handkerchief	1	1-5 times	1	Once
2	Soaked handkerchief	2	6-10 times.	2	More than once
3	Soaked towel	3	11-29 times		
4	Bowl or similar vessel is necessary	4	Daily bleeding		

Table 3: Treatment options for HHT associated epistaxis.

Cautery:

- Electro
- Chemo
- Cryo
- Argonplasma

Hormonal:

- Topical
  - Ostriol
- Systemic
  - Tamoxifen (antiestrogen)
  - Ostradiol
  - Medoxyprogesterone

Antifibrinolytic

- Tranexamic acid
- Ethamsylate

Surgical

- Septodermoplasty
- Closure of the nostril (Modified Young's procedure)

Arterial ligation:

- Ethmoidal (anterior & posterior)
- Maxillary
- External carotid
- Sphenopalatine

Sclerotherapy

Selective arterial embolization

Laser:

- Argon
- KTP
- Nd-YAG
- Diode
- Pulsed-dye

Anti-VEGF

- Bavacizumab
- Thalidomide

Radiotherapy

Table 4: Data Sheet for the Calculation of the Epistaxis Severity Score (ESS) for Hereditary Hemorrhagic Telangiectasia according to Hoag et al.

How often do you TYPICALLY have nose bleeding? (coefficient 0.14)	
0 - Less than monthly	3 - Several per week
1 - Once per month	4 - Once per day
2 - Once per week	5 - Several each day
How long do your TYPICAL nose bleeds last? (coefficient 0.25)	
0 - <1 minute	3 - 16–30 minutes
1 - 1–5 minutes	4 - >30 minutes
2 - 6–15 minutes	
How would you describe your TYPICAL nose bleeding intensity? (coefficient 0.25)	
0 - Not typically gushing	1 - Typically gushing or pouring
Have you every sought medical attention for nose bleeding? (coefficient 0.30)	
0 - No	1 – Yes
Are you anemic (low blood count) currently? (coefficient 0.20)	
0 - No	1 – Yes
Have you ever received a red blood cell transfusion specifically because of nose bleeding? (coefficient 0.31)	
0 - No	1 – Yes

Six questions are answered, the number of the response is multiplied by the respective coefficient and the sum of these gives the raw epistaxis severity score.

Table 5: Indication of intranasal bevacizumab therapy among patients included in paper IV.

Patient nr.	*Period of treatment before bevacizumab*	*Other HHT manifestations*	*Type of previous treatment*	*Indication of bevacizumab treatment*
1	*9 years*	▪ *GI bleeding*	▪ *Laser* ▪ *Argon plasma coagulation* ▪ *Tranexamic acid*	▪ *IFT increase from 3 to 25 in 2 years in spite of increasing the frequency of laser therapy from 2/year to 4 /year.* ▪ *Hb.around 10 in spite of Laser therapy 2-4 times /year.*
2	*1 month*	▪ *Pulmonary hypertension.* ▪ *GI bleeding.*	▪ *Laser*	▪ *Sever bleeding under laser treatment which makes the treatment impossible.* ▪ *Cyclocapron and Tamoxifen are contra indicated because of pulmonary hypertension and valvular heart disease.* ▪ *The patient is treated for pulmonary hypertension with sildenafil which aggravates the epistaxis.*
*3**	*2 years*	▪ *GI bleeding* ▪ *Small PAVM (untreated)*	▪ *Laser* ▪ *Tranexamic acid* ▪ *Tamoxifen*	▪ *IFT increase from 12 to 25 in 2 years in spite of Laser therapy 3-4 times/ year.* ▪ *Tamoxifen had to be stopped because of side effect (vaginal bleeding).* ▪ *The patient refused Septodermoplasy*
4	*9 years*	▪ *PAVM (treated)*	▪ *Laser* ▪ *Tranexamic acid*	▪ *IFT increase from 8 to 15 during the last 3 years in spite of increasing the frequency of laser therapy from 1/year to 4/ year.* ▪ *Bleeding under the laser therapy which makes the therapy ineffective.* ▪ *The patient has a large septal perforation which makes the Septodermoplasty not promising.*
*5**	*20 years*	▪ *PAVM (treated)*	▪ *Septodermoplasty* ▪ *Laser* ▪ *Raloxifen*	▪ *IFT increase from 4 to 11 during the last 2 years in spite of increasing the frequency of laser therapy from 1/year to 2/ year.* ▪ *Hb. between 10 and 11 in spite of Laser therapy 2-3 times /year.*
6	*5 years*	▪ *Hepatic AVM*	▪ *Laser* ▪ *Argon plasma coagulation*	▪ *IFT increase from 3 to 9 during the last 3 years in spite of increasing the frequency of laser therapy from 3/year to 4/ year.* ▪ *The patient refused Septodermoplasy*
*7***	*9 years*	▪ *Migraine*	▪ *Laser* ▪ *Argon plasma coagulation*	▪ *Bleeding under the laser therapy which makes the therapy ineffective.* ▪ *IFT did not go under 7 during the last 3 years in spite of increasing the frequency of laser therapy from 3/year to 4/ year.* ▪ *Hb. around 8 in spite of laser therapy 2-4 times /year.* ▪ *The patient refused Septodermoplasy*
8	*4 years*	▪ *None*	▪ *Laser* ▪ *Tranexamic acid*	▪ *IFT increase from 4 to 10 during the last 3 years in spite of increasing the frequency of laser therapy from 2/year to 3/ year.* ▪ *Bleeding under the laser therapy which makes the therapy ineffective.* ▪ *The patient has a large septal perforation which makes the Septodermoplasty not promising.*

* Patient did not respond to the first dose.

** Patient did not respond to the second dose.

Table 6: QoL of patients in paper III and paper IV

		Average QoL in patients included in paper IV (Pretreatment level) N = 8	Average QoL in patients included in paper III N=66
Health related QoL, SF-36	Physical Functioning	60.0	75.8
	Role Physical	45.3	55.5
	Bodily Pain	71.1	71.5
	General Health	48.6	60.8
	Vitality	36.9	50.2
	Social Functioning	62.5	80.5
	Role Emotional	45.0	70.2
	Mental Health	53.5	77.8
	PCS	42.7	44.3
	MCS	40.0	50.5
Overall QoL		5.8	7
Disease specific QoL		6.3	4.7

P=0.002 (t-test)

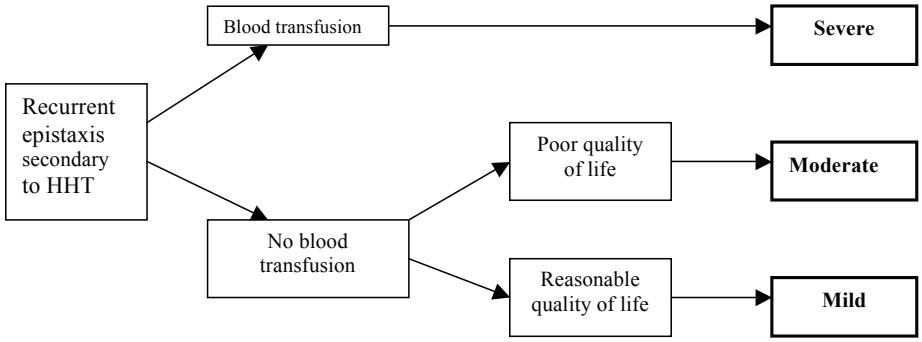
Table 7: The age and gender distribution of the patients with the pre-and post-treatment epistaxis grades and hemoglobin level.

Patient nr.	*Gender*	*Age in years*	*IFT epistaxis grading*		*Intensity (I)*		*Frequency (F)*		*ESS epistaxis grading*		*Hemoglobin g/dl*		*Observation period (weeks)*
			Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	
1	*F*	*68*	*25*	*3*	*5*	*3*	*5*	*1*	*6.44*	*2.61*	*10.1*	*12.0*	*12*
2	*M*	*43*	*12*	*2*	*7*	*2*	*5*	*3*	*5.52*	*1.96*	*11.1*	*14.0*	*10*
3	*F*	*53*	*25*	*2*	*3*	*1*	*6*	*4*	*8.25*	*2.49*	*13.2*	*15.4*	*8*
4	*F*	*36*	*15*	*4*	*5*	*3*	*5*	*3*	*4.70*	*3.02*	*11.7*	*13.4*	*8*
5	*F*	*71*	*11*	*4*	*6*	*1*	*5*	*2*	*6.98*	*2.49*	*10.4*	*11.1*	*8*
6	*M*	*53*	*9*	*3*	*5*	*1*	*4*	*3*	*4.98*	*2.49*	*11.0*	*17.1*	*10*
7	*F*	*69*	*7*	*7*	*4*	*3*	*5*	*6*	*4.98*	*4.98*	*8.4*	*8.0*	*10*
8	*M*	*59*	*10*	*3*	*6*	*1*	*4*	*3*	*6.20*	*2.49*	*8.5*	*13.0*	*10*
Mean		*56.5*	*14.3*	*3.5*	*5.1*	*1.9*	*4.9*	*3.1*	*6.00*	*2.82*	*10.6*	*13.0*	*9.5*
P-value			*0.007*		*0.02*		*0.01*		*0.001*		*0.01*		

Appendix 1

The grading scales which were in use at the time of running paper I

1. Grading epistaxis according to Lund et al.



2. Grading epistaxis according to Reibez et al.

Severity of epistaxis	Frequency of epistaxis	No. of transfusions
Mild	**Few episodes / week**	**None**
Moderate	**1-2 time / day**	**< 10/ lifetime**
Severe	**Daily epistaxis lasting greater than 30 min**	**> 10/ lifetime**

3. Grading according to Bergler et al.

Intensity of bleeding	Frequency of bleeding
Grade 1: slight stains on the handkerchief	**Grade 1: less than once a week**
Grade 2: soaked handkerchief	**Grade 2: a few times a week**
Grade 3: bowl or similar utensil necessary	**Grade 3: more than once a day**

4. Grading according to Pagella et al.

Necessity of blood transfusion	
1	None
2	< 10 in lifetime
3	> 10 in lifetime
Frequency of epistaxis	
1	Less than once a week
2	Several times a week
3	Several times a day
Length of epistaxis	
1	< 10 min
2	Between 10 min and 30 min
3	> 30 min

Appendix 2

Expert opinion questionnaire: Grading of epistaxis in Hereditary Hemorrhagic Telangectesia (HHT).

So far different grading systems for epistaxis in HHT exist, for example from Bergler et al[1] or Rebeiz et al[2]. The aim would be a scale, which can serve as a proposal for a better grading system.

1) Should a grading system be divided up into two scales? For example: one scale for frequency and another scale for severity.
   □ One scale (including one multi-item scale) □ More than one scale

2) Ideally, should a grading system consist of a relative scale or an absolute scale?
   □ Relative

   Grade I mild
   Grade II moderate
   Grade III severe

   □ Absolute

   Grade O no bleeding
   Grade 1 mild
   Grade 2 moderate
   Grade 3 severe
   Grade 4 intractable

3) Is the need for blood transfusion an important parameter? Mind the patient may bleed simultaneously from other sites than the nose.
   □ Yes □ No

4) Do you think, for research purposes, a grading system should be easy to understand for the patient? For example when the patient is using a diary.
   □ Yes □ No

5) Should a grading system focus on the duration of one single bleeding episode or should a grading system focus on a definite time period like for example one month observation time?
   □ Focus on one single bleeding episode □ Focus on a definite time period

- Do you agree that anonymized data from this questionnaire can be used in a publication?
  □ Yes □ No
- Do you agree that your name will be mentioned in acknowledgements of a publication on grading of epistaxis in HHT?
  □ Yes □ No

- General comments:

[1] Bergler W, Götte K. Hereditary hemorrhagic telangiectasias: a challenge for the clinician. *Eur. Arch. Otorhinolaryngol.* 1999; 256:10–15.

[2] Rebeiz EE, Bryan DJ, Ehrichman RJ, Shapshay SM . Surgical management of life threatening epistaxisin Osler- Weber- Rendu disease. *Ann.plast.surg* 1995; 35:208-213.

Appendix 3

Questionnaire for evaluation of the severity of nosebleed associated with Hereditary Hemorrhagic Telangiectasia. According to IFT system

English version

Name:

Date of birth:

- It is optional answer the questionnaire.
- Please tick next to the answer that best fits what you have experienced.
- The questions below are for research reason.
- Please answer all questions.
- If you have any questions, ask your physician or call 23076202.

1) During the past 4 weeks, how many times you got spot of blood from the nose or dripped a few drops of blood from nose?

□ None
□ 1-5 times
□ 6-10 times
□ 11 to 27 times
□ Daily or more

2) During the past 4 weeks, how many times you got blood soaked handkerchief?

□ None
□ 1-5 times
□ 6-10 times
□ 11 to 27 times
□ Daily or more

3) During the past 4 weeks, how many times you got blood soaked towel?

□ None
□ 1-5 times
□ 6-10 times
□ 11 to 27 times
□ Daily or more

4) During the past 4 weeks, low many times you got bleeding that fills so much as a bowl (1/2 liter) of blood?

□ None
□ 1-5 times
□ 6-10 times
□ 11 to 27 times
□ Daily or more

5) During the past 4 weeks, how many times did you get a blood transfusion?

□None
□ Once
□ Several times

Spørreskjema for evaluering av alvorlighet av neseblødning ved Osler sykdom. *Norwegian version*

Navn:
Fødselsdato:

- Det er frivillig å svare på spørreskjema.
- Sett kryss ved det svaralternativet som passer best til det du har opplevd.
- Spørsmålene nedenfor er kun til forskningsgrunn.
- Vær så snill svar alle spørsmål.
- Hvis du har spørsmål, spør behandlende lege eller ring 23076202.

1) I løpet siste 4 uker, hvor mange ganger fikk du blodflekk fra nesen på lommetørkle eller dryppet noen dråper blod fra nesen?
   - ☐ Ingen
   - ☐ 6-10 ganger
   - ☐ 11-27 ganger
   - ☐ 11-27 ganger
   - ☐ Daglig eller flere

2) I løpet siste 4 uker, hvor mange ganger fikk du blodgjennomtrukket lommetørkle?
   - ☐ Ingen
   - ☐ 6-10 ganger
   - ☐ 11-27 ganger
   - ☐ 11-27 ganger
   - ☐ Daglig eller fler

3) I løpet siste 4 uker, hvor mange ganger fikk du blodgjennomtrukket håndkle?
   - ☐ Ingen
   - ☐ 6-10 ganger
   - ☐ 11-27 ganger
   - ☐ 11-27 ganger
   - ☐ Daglig eller fler

4) I løpet siste 4 uker, hvor mange ganger fikk du blødning som fyller så mye som en bolle (1/2 liter) blod?
   - ☐ Ingen
   - ☐ 6-10 ganger
   - ☐ 11-27 ganger
   - ☐ 11-27 ganger
   - ☐ Daglig eller flere

5) I løpet av siste 4 uker, hvor mange ganger fikk du blodoverføring?
   - ☐ Ingen
   - ☐ En gang
   - ☐ Flere ganger

Appendix 4

Symptom specific questionnaire for quality of life in patients with HHT.

English version

Dear participant, this questionnaire was developed, to collect symptoms from several diseases within the field of ear nose and throat. It is possible, that some questions will not be applicable in your case. Please mark "not applicable" in this situation. Please fill in the questionnaire completely.

1. Please give three symptoms, which burdens you very much (start with the one which burdens you most).

2. Please give three aspects of your life (like job, time off, working in the garden etc.) which are affected very much due to the disease (start with the aspect, which affects most).

3. Please give three very important activities, which you cannot perform due to the disease (start with the most important).

4. The disease has influence on my family planning.
Yes No Not applicable

5. Please mark the most important symptom (please only one)
-nosebleed
-visible red spots on the skin
-vessel anomalies in the lung
-vessel anomalies in the liver
-bleeding in the gut, the fact that the disease is inherited
-blockage of the nose, disturbances of sense of smell
-hearing disorders
-sinusitis
-headaches
-running nose
-not applicable

6. How much is your quality of life affected? 1 means no affection and 10 means highest possible affection.
1 2 3 4 5 6 7 8 9 10

7. Which problems should be adressed in scientific research in the future?
-development of gene therapy
-development of new therapies for nosebleed
-control of anomalies of vessels in internal organs
-genetic counseling, development of early diagnostic tests
- other:

8. Which is the most bothering therapy in relation to the disease:
-packing of the nose
-blood transfusion
-nasal ointment, oral iron supplements
-tranplantation of nasal mucosa (Saunders nasoplasty)
-laser therapy, removal of polyps as an outpatient
-surgery of the paranasal sinuses in general anesthesia
-not applicable.

9. How much time you need to care for the nose each day.
0-15 min, 15-30 min, 30-45 min, 45-60 min, more than 60 min

10. How often you get treatment (each contact with a doctor)
-more than once per month
-every month
-several times per year

-once per year
-less than once per year

11. Do you have pain and is this connected to distinct circumstances?
(keywords)

12. Which aspects have not yet been mentioned?
(keywords)

13. Repeated nosebleeds is bothering me.
Yes No Not applicable

14. I'm worrying that I do have, apart from nosebleeds, the risk of other disorders.
Yes No Not applicable

15. How would you estimate the nose bleedings?
Not applicable
Intensity mild (a few drops in a handkerchief)
moderate (soaked handkerchief)
severe (more than one handkerchief)
Frequency several times a day
several times a week
several times a months

16. Imagine you would not have any nosebleeds any more. How would you estimate your quality of life on a scale from 1 (no affection) to 10 (highest possible affection)
1 2 3 4 5 6 7 8 9 10

17. How many times you were admitted to hospital and how many days as an in-patient you spent during the last 12 months.
_____ times admitted to hospital
_____ days as in-patient

18. When was the diagnosis HHT found (which year)?
_____

Thank you for your cooperation !

Symptomspesifikk spørreskjema for evaluering av livskvaliteten hos pasienter med HHT. *Norwegian version*

1. Kan du nevne 3 symptomer av lidelsen, som påvirke deg mest (begynn med det som påvirker mest)

2. Kan du nevne 3 områder av livet ditt (for eksempel yrke, fritid, hagearbeid eller lignende) som blir påvirket mest av lidelsen (begynn med det som påvirker mest).

3. Kan du neven 3 aktiviteter, som ikke kan gjøres på grunn av lidelsen (begynn med denne aktiviteten som er viktigst for deg).

4. Lidelsen påvirker familieplanlegging.
   - ja - nei - er ikke aktuelt for meg

5. Sett kryss for symptomet, som påvirker deg mest (kun ett kryss)
   - neseblødning
   - synlige blodkarforandringer på huden
   - arterio-venøse malformasjoner i lunge
   - arterio-venøse malformasjoner i lever
   - blødniger fra mave-tarm trakt
   - arvelighet av lidelsen
   - nesetetthet
   - nedsatt luktesans
   - nedsatt hørsel
   - betennelse i bihulene
   - hodepine
   - forkjølelse og renning fra nese
   - ikke aktuelt for meg

6. Hvor sterkt er livskvaliteten påvirket på en skala mellom 1 og 10? (1= ingen påvirkning, 10=maksimal påvirkning)

7. Hvilket problem i sammenheng med lidelsen burde forskes på mer i fremtiden? (ikke mer enn 3 kryss)
   - genterapi
   - behandling av neseblødning
   - behandling av arterio-venøse malformasjoner i indre organer
   - genetisk veiledning
   - ny metoder for å finne sykdommen tidligere
   - annet problem: …

8. Hva er den mest ubehagelige behandling for denne lidelsen?
   - nesetamponade
   - blodtransfusjon
   - nesesalve
   - operasjon med Saunders plastikk
   - laserbehandling
   - fjerning av polypper på dagkirurgisk avdeling
   - bihulekiurgi i full narkose
   - er ikke aktuelt for meg

9. Hvor mye tid trenger du for å pleie nesen per dag?
   - 0-15 min - 15-30 min - 30-45 min - 45-60 min - mer enn 60 min

10. Hvor ofte blir du behandlet for denne lidelsen?
   - oftere - i måned - mange ganger i året - i året - sjeldnere

11. Har du vond? Hvis ja, når?

12. Hvilke aspekter av livet ditt ble ikke tatt opp i spørreskjema?

13. På grunn av neseblødningen føler jeg meg uvel.
- ja - nei - er ikke aktuelt for meg

14. Jeg er redd for at jeg muligens har andre forandringer ved siden av neseblødninger.
- ja - nei - er ikke aktuelt for meg

15. Hvor mye og hvor ofte blør det fra nesen?
Intensitet: - lite (noe dråper i et klut)
- moderat (hele kluten full)
- mye (mer enn et klut)
Frekvens - mange ganger om dagen
- mange ganger i en uke
- mange ganger i en måned

16. Tenk du hadde ingen neseblødning lenger. Hvor ville du sette kryss på en skala mellom 1 og 10. 1=ingen problemer og 10=maksimale problemer
- ikke aktuelt for meg
- 1 - 2 - 3 - 4 - 5 - 6 - 7
-8 - 9 - 10

17. Hvor mange ganger har du vart innlagt på sykehuset på grunn av lidelsen i løpet av de siste 12 måneder? Hvor mange dager var du innlagt til sammen?
…….. x innlagt
…….. dager tilsammen

18. I hvilket år ble sykdommen oppdaget hos deg?
……..

Takk for medarbeidet!

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Errata List

1. The word “system” in page 10, line 7, first paragraph has been added.
2. The word “hemorrhage” after the word “or” in page 12, line 9, second paragraph has been added.
3. The word “hemorrhage” after “due to” in page 17, line 3 of “Prognosis” paragraph has been added.
4. The word “three” as been changed to “two” in page 54, line 5.